OXFORD UNIVERSITY PRESS
American Journal of
EPIDEMIOLOGY

Volume 155(7) 1 April 2002 pp 629-635

Plasma Concentrations of Polychlorinated Biphenyls and the Risk of Breast Cancer: A Congener-specific Analysis

[Original Contributions]

Demers, Alain[1]; Ayotte, Pierre[2,3]; Brisson, Jacques[3,4]; Dodin, Sylvie[2,5]; Robert, Jean[4]; Dewailly, Éric[2,3]

[1]Department of Preventive Oncology and Epidemiology, CancerCare Manitoba, Winnipeg, Manitoba, Canada.

[2]Unité de Recherche en Santé Publique, Centre de Recherche du CHUQ (CHUL), Beauport, Québec, Canada.

[3]Département de Médecine Sociale et Préventive, Faculté de Médecine, Université Laval, Ste-Foy, Canada.

[4]Unité de Recherche en Santé des Populations et Centre des Maladies du Sein Deschênes-Fabia, Hôpital Saint-Sacrement, Centre Hospitalier Affilié Universitaire de Québec, Québec, Canada.

[5]Unité de Recherche en Endocrinologie de la Reproduction, Centre de Recherche du Pavillon Saint-François-d'Assise, Québec, Canada.

Received for publication May 9, 2001, and accepted for publication October 11, 2001.

Correspondence to Dr. Pierre Ayotte, Unité de Recherche en Santé Publique, Centre de Recherche du CHUQ (CHUL), 2400 d'Estimauville, Beauport, Quebec, Canada G1E 7G9 (e-mail: pierre.ayotte@crchul.ulaval.ca).

Outline

Graphics

Abstract

Some reports indicate that exposure to specific polychlorinated biphenyl (PCB) congeners is related to breast cancer risk. The authors recruited participants in a case-control study from October 1994 to March 1997 to assess the relation between breast cancer risk and concentrations of 14 PCB congeners measured in plasma lipids by high-resolution gas chromatography. Participants were incident cases of breast cancer ($n = 314$) and controls ($n = 523$) from the Quebec City region (Canada). Compared with controls, cases had significantly higher concentrations of PCB 99 ($p = 0.02$), PCB 118 ($p = 0.03$), and PCB 156 ($p = 0.006$). Associations were found between breast cancer risk and either PCB 118 (odds ratio (OR) = 1.60, 95% confidence interval (CI): 1.01, 2.53; fourth vs. first quartile) or PCB 156 (OR = 1.80, 95% CI: 1.11, 2.94; fourth vs. first quartile) concentration. Breast cancer risk was also associated with a total concentration of the three mono-*ortho*-substituted congeners 105, 118, and 156 expressed as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxic equivalents (OR = 2.02, 95% CI: 1.24, 3.28; fourth vs. first quartile). These results suggest that exposure to dioxin-like PCBs increases breast cancer risk. Alternatively, the results may be explained by differences between cases and controls regarding metabolic pathways involved in the biotransformation of both mono-*ortho* PCBs and estrogens.

Abbreviations: CI, confidence interval; odds ratio; PCB, polychlorinated biphenyl; TEQ, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxic equivalents.

The relation between exposure to polychlorinated biphenyls (PCBs) and breast cancer has been addressed in numerous epidemiologic studies since the early 1990s. Most studies that used the sum of all PCB congeners as the measure of exposure did not report an association with the risk of breast cancer (1–7). However, a series of recent studies that examined the relations with individual PCB congeners or groups of congeners have yielded conflicting results (8–20).

PCBs constitute a family of 209 possible congeners that were extensively used in industrial and commercial products from 1930 to 1980. PCBs were commercialized as mixtures (Aroclor 1254 (Monsanto Chemical Company, St. Louis, Missouri), Clophen 60 (Farbenfabricken Bayer GmbH, Leverkusen, Germany), and so on) usually composed of 50–70 different congeners (21). A total of 132 congeners have been identified in commercial products, some of them being present in only one mixture and others in all of them (22). Although their use was banned 20 years ago in Canada and the United States, they are still found in the environment and in the food chain, especially in fatty foods (23). This results from their great stability and continued release into the environment, because of improper storage, disposal, and ongoing use in some parts of the world. Biologic half-lives of several years have been documented in humans for the most persistent congeners (24), resulting in their accumulation with age in body fat, including adipose tissue (25), plasma lipids (26), and milk fat (27).

Several mechanisms might be involved in the modulation of breast cancer risk by specific PCB congeners. First, PCBs (lower chlorinated) and some hydroxylated metabolites display estrogenic properties (28–30). Second, mono- and non-*ortho*-substituted congeners share some structural similarities with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and can bind the aryl hydrocarbon receptor (31). The consequences of activation of the aryl hydrocarbon receptor pathway on breast cancer risk are, however, not clear. On the one hand, dioxin-like compounds elicit a broad spectrum of antiestrogenic activities (32–36) and may reduce breast cancer risk. On the other hand, activation of the aryl hydrocarbon receptor leads to induction of CYP1A1/A2 and CYP1B1 expression, which in turn could increase the biotransformation of estradiol to catechol estrogens (37–42), the latter exhibiting genotoxic properties (43). Di-*ortho*-substituted congeners

induce a different profile of biotransformation enzymes (CYP2B1/B2 and CYP3A), similar to that induced by phenobarbital (37, 44, 45), and these enzymes are also involved in the metabolism of estradiol (39, 45, 46). Mono-*ortho* PCBs are both phenobarbital- and dioxin-like inducers and are therefore referred to as mixed inducers (37). A recent case-control study reported that concentrations of two mono-*ortho* PCBs in breast adipose tissue were associated with breast cancer risk (17).

We previously reported that exposure to total PCBs, as estimated by the concentration of the most abundant and persistent congener in plasma lipids (PCB 153), was not associated with breast cancer risk (47). To test the hypothesis that exposure to specific PCB congeners may be related to breast cancer, we examined the relation between the disease risk and the plasma lipid concentrations of 14 individual PCB congeners, with a special focus on mono-*ortho* PCB congeners that display dioxin-like activity. The risk was examined separately in premenopausal and postmenopausal women in view of recent results suggesting that the menopausal status may modify the effect of PCBs on breast cancer risk (17).

MATERIALS AND METHODS

Population

From October 1994 to March 1997, 315 women with histologically confirmed infiltrating primary breast cancer and 219 controls were recruited in four hospitals of the Quebec City area (Quebec, Canada). A second control group included 307 women randomly selected from the general population files of the Régie de l'Assurance maladie du Québec. Cases and controls were matched for age (5-year age groups) and region of residence (rural/urban). Cases were excluded if they showed distant metastasis at diagnosis or if they had a previous history of breast cancer or any other cancer, except cervical intraepithelial neoplasm or basocellular skin cancer. Only women without a history of cancer were recruited as controls. All participants had to be aged between 30 and 70 years and to be residents of the Quebec City area. Hospital controls had, in addition, to be free of gynecologic illnesses; they were admitted for digestive surgery (50 percent), orthopedic surgery (25 percent), vascular surgery (14 percent), or other surgeries (11 percent). Participation rates were 91 percent for cases, 89 percent for hospital controls, and 47 percent for population controls. One case and three controls for whom the levels of organochlorines in plasma were not available were removed from the database.

Blood samples were obtained from cases and hospital controls after surgery and for cases prior to the initiation of chemotherapy or radiotherapy. A research nurse visited population controls at their residence, and blood sampling was performed during this visit. Information on lifestyle, dietary habits, and reproductive history was obtained by telephone interview. Women were categorized as menopausal if they had no menses during the last 6 months. Review boards from Université Laval and the participating hospitals have approved the study proposal, and informed consent was obtained from all women prior to their enrollment.

Laboratory analyses

Fourteen PCB congeners (International Union for Pure and Applied Chemistry (IUPAC) numbers 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187) were quantified in plasma samples by high-resolution gas chromatography with electron-capture detection (47). The detection limit for each congener was 0.02 μg/liter. The average percentage of recovery for all congeners was greater than 95 percent, and the between-day precision ranged from 3.3 percent to 7.0 percent. The total plasma lipid content was determined by enzymatic methods, and

concentrations of PCBs are reported in μg/kg of plasma lipids.

Mono-*ortho*-substituted congeners display some affinity for the aryl hydrocarbon receptor, and a toxicity scale relative to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, the most potent aryl hydrocarbon receptor agonist, was established to calculate the total concentration of dioxin-like compounds in a mixture. A total concentration of mono-*ortho* congeners, expressed as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxic equivalents (TEQ), was computed by adding up the weighed concentration of each congener according to its respective toxic equivalency factor, which was 0.0001 for PCB 105 and PCB 118 and 0.0005 for PCB 156 (48).

Statistical analysis

An analysis of variance was conducted to compare the mean concentrations of PCB congeners between cases and controls. The PCB concentrations in plasma lipids displayed lognormal distributions, and therefore all statistical analyses were performed using the natural logarithm of PCB concentrations. A concentration equal to half of the detection limit was assumed for samples with organochlorine levels below the detection limit. Statistical analyses were not performed for congeners that were detected in less than 70 percent of the women.

Point and interval estimation of the odds ratio was based on unconditional logistic regression analysis. Quantile limits of PCB plasma concentrations were based on the distribution observed among controls. Risks were always calculated in relation to the lowest category. Age (30–<40, 40–<50, 50–<60, >=60 years) and region of residence (rural/urban) were included in all multivariate models because cases and controls were frequency matched for these variables. The other variables evaluated as confounders were as follows: body mass index (weight (kg)/height $(m)^2$), total energy consumed, alcohol consumption, age at first cigarette, number of reproductive years, age at first child, total breastfeeding duration, use of oral contraceptive, use of hormone therapy, first degree family history of breast cancer, and history of benign breast disease. A variable was considered as a confounder when its inclusion in the model modified the odds ratio (adjusted for age and region of residence) by more than 10 percent. Characteristics of cases and controls were compared using Student's *t* tests for continuous variables or chi-squared tests for categorical variables. All statistical analyses were performed using SAS version 6.12 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Population and hospital controls exhibited similar characteristics, with the exception that population controls showed more fertile years ($p = 0.003$) and a smaller body mass index ($p = 0.0001$). Furthermore, the concentrations of organochlorines were comparable in both groups, and the associations between organochlorine exposure and breast cancer risk were comparable, regardless of the control group used for risk calculation (47). Consequently, both control groups were combined for the present statistical analyses. Cases and controls did not differ with regard to most characteristics presented in table 1. Family history of breast cancer and history of benign breast disease were reported more frequently by cases than controls ($p = 0.002$ and $p = 0.001$, respectively).

TABLE 1. Selected characteristics of female breast cancer cases and controls, Quebec, Canada, 1994–1997

Characteristic	Cases (n = 314)	Controls (n = 523)
Age (years) (mean, SD*)	53 (9)	52 (10)
Age at menarche (years) (mean, SD)	13 (5)	13 (2)
No. of fertile years (mean, SD)	32 (7)	30 (8)
Age at birth of first child (years) (mean, SD)†	25 (4)	25 (4)
No. of deliveries (mean, SD)	2.2 (2)	2.3 (2)
Body mass index (kg/m²) (mean, SD)	25 (4)	25 (4)
Menopausal women (%)‡	70	65
Breastfed more than 6 months (%)†	12	10
Ever use contraceptive (%)	68	63
Ever use hormone replacement (%)	42	36
History of breast cancer in first degree relatives (%)§	22	14
History of benign breast disease (%)¶	34	18

* SD, standard deviation.
† Among parous women only.
‡ A total of 51% of menopausal women had a natural menopause, 29% had a hysterectomy without ovariectomy, and 18% had uni- or bilateral ovariectomy (2% unknown).
§ Data for this variable were available for 310 cases and 518 controls.
¶ Cyst puncture or benign breast illnesses investigated with surgery.

TABLE 1. Selected characteristics of female breast cancer cases and controls, Quebec, Canada, 1994–1997

Table 2 presents the concentrations of PCB congeners in plasma samples of cases and controls. PCB 28, PCB 52, PCB 101, PCB 105, and PCB 128 were detected in less than 70 percent of the women and were excluded from statistical analyses. Pearson's correlation coefficients among concentrations of the various congeners detected in 70 percent or more of the samples ranged from 0.29 to 0.96 ($p < 0.0001$; $n = 837$). Congeners 138, 153, and 180 showed the highest concentrations, and all three represented 60 percent of the total PCB concentration in both cases and controls. No difference was observed between cases and controls for these major congeners. However, the concentrations of PCB 99 ($p = 0.02$), PCB 118 ($p = 0.03$), and PCB 156 ($p = 0.006$) were found in slightly greater concentrations in cases than in controls.

TABLE 2. Plasma lipid concentrations of polychlorinated biphenyl congeners* in female breast cancer cases and controls, Quebec, Canada, 1994–1997

PCB† no.	Cases (n = 314)			Controls (n = 523)			p value‡
	Mean§ (SE†)	Median	% detected	Mean (SE)	Median	% detected	
28	4.4 (3.4)	4.0	69	5.1 (0.6)	4.2	65	
52	3.8 (0.1)	3.4	45	3.4 (0.1)	3.0	38	
99	10.8 (0.5)	9.9	98	9.6 (0.5)	9.3	97	0.02
101	3.3 (0.1)	3.0	29	2.7 (0.1)	2.7	22	
105	4.7 (0.3)	4.4	64	4.2 (0.3)	4.0	61	
118	17.7 (0.9)	15.8	100	15.7 (0.8)	14.3	99	0.03
128			4			1	
138	38.1 (1.3)	37.2	100	35.4 (1.2)	35.5	100	0.21
153	54.1 (1.7)	55.0	100	51.9 (1.5)	50.7	100	0.53
156	8.5 (0.3)	8.2	99	7.7 (0.2)	7.6	99	0.006
170	13.3 (0.5)	12.9	100	12.5 (0.4)	12.3	100	0.27
180	32.9 (1.4)	32.1	100	31.1 (1.3)	30.2	100	0.44
183¶	4.8 (0.2)	4.4	87	4.7 (0.2)	4.1	83	0.28
187	10.5 (0.6)	9.8	99	9.9 (0.5)	9.3	100	0.55

* Concentrations expressed as μg/kg
† PCB, polychlorinated biphenyl; SE, standard error
‡ Tests were not performed for congeners that were detected in less than 70% of the women.
§ Arithmetic mean adjusted for age, region of residence, body mass index, breastfeeding, and benign breast disease
¶ Data missing for 22 cases and 24 controls

TABLE 2. Plasma lipid concentrations of polychlorinated biphenyl congeners* in female breast cancer cases and controls, Quebec, Canada, 1994–1997

A statistically significant association was found between plasma concentrations of either PCB 118 (odds ratio (OR) = 1.60, 95 percent confidence interval (CI): 1.01, 2.53; fourth vs. first quartile) or PCB 156 (OR = 1.80, 95 percent CI: 1.11, 2.94; fourth vs. first quartile) and breast cancer risk (table 3). These associations appeared stronger in premenopausal than in postmenopausal women, although the menopausal status was not an effect modifier in this data set ($p > 0.05$).

TABLE 3. Odds ratios of female breast cancer according to plasma lipid concentrations of polychlorinated biphenyl congeners,* by menopausal status, Quebec, Canada, 1994–1997

PCB† no.	Quartile‡	All women			Premenopausal women			Postmenopausal women		
		Cases/controls	OR§	95% CI	Cases/controls	OR	95% CI	Cases/controls	OR	95% CI
99	<6.5	70/131	1.00		29/68	1.00		41/63	1.00	
	6.5–<9.3	80/131	1.20	0.79, 1.82	28/56	1.52	0.78, 2.96	51/75	1.06	0.61, 1.82
	9.3–<12.9	77/130	1.27	0.83, 1.96	23/41	1.64	0.79, 3.41	54/89	1.07	0.62, 1.86
	≥12.9	87/131	1.33	0.86, 2.07	13/17	1.78	0.71, 4.42	74/114	1.11	0.65, 1.89
118	<9.4	68/131	1.00		35/74	1.00		33/57	1.00	
	9.4–<14.3	64/130	0.90	0.58, 1.39	26/51	0.94	0.48, 1.82	38/79	0.89	0.49, 1.62
	14.3–<22.1	76/132	1.12	0.73, 1.74	18/46	0.72	0.35, 1.48	60/86	1.35	0.75, 2.41
	≥22.1	104/130	1.60	1.01, 2.53	11/15	2.87	1.13, 7.31	89/119	1.51	0.84, 2.69
138	<26.9	65/131	1.00		29/73	1.00		40/58	1.00	
	26.9–<35.5	74/131	1.06	0.69, 1.62	25/62	1.00	0.52, 1.93	49/69	1.04	0.59, 1.83
	35.5–<46.9	85/130	1.17	0.76, 1.80	31/32	2.10	1.05, 4.21	54/98	0.82	0.47, 1.43
	≥46.9	86/131	1.18	0.75, 1.85	9/15	1.18	0.43, 3.25	77/116	1.09	0.58, 1.73
153	<38.7	66/130	1.00		30/75	1.00		36/55	1.00	
	38.7–<50.7	71/132	0.97	0.63, 1.50	23/57	0.88	0.44, 1.74	48/75	0.95	0.54, 1.69
	50.7–<65.9	85/131	1.16	0.75, 1.79	26/36	1.39	0.68, 2.86	59/95	0.95	0.53, 1.69
	≥65.9	92/130	1.22	0.78, 1.92	15/14	1.98	0.79, 4.96	77/116	1.01	0.58, 1.76
156	<5.8	50/130	1.00		25/86	1.00		25/44	1.00	
	5.8–<7.6	83/131	1.44	0.91, 2.26	27/47	1.73	0.86, 3.48	56/84	1.13	0.59, 2.04
	7.6–<9.8	80/132	1.44	0.90, 2.31	26/32	2.59	1.19, 5.64	55/100	0.94	0.50, 1.77
	≥9.8	101/130	1.80	1.11, 2.94	17/17	2.90	1.18, 7.15	84/113	1.30	0.69, 2.43
170	<9.5	54/131	1.00		26/85	1.00		29/46	1.00	
	9.5–<12.3	88/131	1.35	0.86, 2.12	28/40	1.54	0.74, 3.21	60/91	1.01	0.56, 1.84
	12.3–<15.7	74/131	1.13	0.71, 1.82	25/38	1.61	0.75, 3.48	49/93	0.79	0.42, 1.47
	≥15.7	98/130	1.46	0.90, 2.37	16/19	1.99	0.79, 4.99	82/111	1.11	0.60, 2.04
180	<23.4	56/131	1.00		27/86	1.00		29/45	1.00	
	23.4–<30.2	75/130	1.20	0.76, 1.90	24/50	1.29	0.63, 2.62	55/80	0.99	0.53, 1.84
	30.2–<40.0	96/132	1.37	0.86, 2.19	28/27	2.40	1.10, 5.27	68/105	0.93	0.50, 1.73
	≥40.0	83/130	1.17	0.70, 1.93	15/19	1.96	0.78, 4.95	68/111	0.83	0.44, 1.60
183	<2.9	54/125	1.00		24/71	1.00		30/54	1.00	
	2.9–<4.1	77/126	1.29	0.82, 2.01	27/54	1.37	0.69, 2.72	50/72	1.18	0.66, 2.13
	4.1–<5.6	82/126	1.41	0.89, 2.24	25/33	1.84	0.85, 3.98	57/93	1.14	0.63, 2.05
	≥5.6	80/125	1.35	0.84, 2.16	10/17	1.35	0.51, 3.59	70/108	1.19	0.67, 2.12
187	<6.9	55/130	1.00		26/75	1.00		29/55	1.00	
	6.9–<9.3	88/132	1.35	0.87, 2.09	26/59	1.04	0.52, 2.06	62/73	1.50	0.84, 2.69
	9.3–<12.4	87/130	1.34	0.85, 2.12	23/28	1.96	0.90, 4.27	64/102	1.10	0.61, 1.99
	≥12.4	86/131	1.33	0.83, 2.13	19/20	1.89	0.81, 4.42	67/111	1.10	0.61, 1.99

* Concentrations expressed as μg/kg.
† PCB, polychlorinated biphenyl; OR, odds ratio; CI, confidence interval.
‡ Polychlorinated biphenyl concentrations were divided into quartiles according to the distribution among the controls.
§ Odds ratios were adjusted for age, region of residence, body mass index, personal history of benign breast disease, and breastfeeding duration.

TABLE 3. Odds ratios of female breast cancer according to plasma lipid concentrations of polychlorinated biphenyl congeners,* by menopausal status, Quebec, Canada, 1994–1997

The mean total concentration of mono-*ortho* congeners PCB 105, PCB 118, and PCB 156 was significantly higher in cases than in controls (6.4 (standard error, 0.2) vs. 5.8 (standard error, 0.2) ng of TEQ/kg of lipids; $p = 0.005$, adjusted for age, region of residence, body mass index, history of benign breast disease, and breastfeeding duration). Higher concentrations of these congeners were associated with the risk of developing breast cancer (OR = 2.02, 95 percent CI: 1.24, 3.28; fourth vs. first quartile) (table 4). Again, this association appeared stronger in premenopausal women, but the menopausal status was not an effect modifier ($p = 0.32$).

TABLE 4. Odds ratios of female breast cancer according to plasma lipid concentrations of mono-*ortho*-polychlorinated biphenyl congeners,* by menopausal status, Quebec, Canada, 1994–1997

Quartile limits†	All women			Premenopausal women			Postmenopausal women		
	Cases/controls	OR‡,§	95% CI‡	Cases/controls	OR	95% CI	Cases/controls	OR	95% CI
<4.2	49/131	1.00		27/82	1.00		22/49	1.00	
4.2–<5.7	85/130	1.63	1.04, 2.55	31/57	1.29	0.66, 2.52	54/73	1.78	0.95, 3.36
5.7–<7.4	78/132	1.45	0.90, 2.32	21/29	1.83	0.84, 4.00	57/103	1.30	0.69, 2.46
≥7.4	102/130	2.02	1.24, 3.28	15/14	2.60	1.02, 6.63	87/116	1.84	0.98, 3.46

* The total concentration of three mono-*ortho* congeners (nos. 105, 118, and 156) was expressed in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxic equivalents (ng/kg).

† Concentrations are divided into quartiles according to the distribution among the 526 controls.

‡ OR, odds ratio; CI, confidence interval.

§ Odds ratios were adjusted for age, region of residence, body mass index, personal history of benign breast disease, and breastfeeding duration.

TABLE 4. Odds ratios of female breast cancer according to plasma lipid concentrations of mono-*ortho*-polychlorinated biphenyl congeners,* by menopausal status, Quebec, Canada, 1994–1997

Among the 299 cases with available information on tumor diameter at the time of pathologic analysis, 142 (47 percent) had tumors equal to or greater than 2 cm. Of the 273 cases who had axillary excision, 118 (43 percent) showed axillary lymph node involvement. No association was found between PCB congeners and both markers of breast cancer prognosis.

DISCUSSION

Results of the present study suggest that exposure to dioxin-like mono-*ortho* PCB congeners increases the risk of breast cancer. Weighed total concentrations of three mono-*ortho* congeners (PCB 105, PCB 118, PCB 156), expressed in TEQ, were associated with breast cancer risk. PCB 118 and PCB 156 were also individually related to risk, but the most abundant and persistent PCB congeners (PCB 138, PCB 153, PCB 180) were not linked to breast cancer risk.

The relation between PCBs and breast cancer has been addressed using different measures of exposure in previous studies. Most studies that used the total PCB concentration as the measure of exposure reported no association with breast cancer risk (1–7, 12, 15). Recent studies investigated the relations between breast cancer risk and PCB congeners either considered individually or grouped according to common characteristics. Zheng et al. (13) conducted a case-control study involving 475 cases and 502 controls, who were either randomly selected from residents living in the same county or patients from the same hospital (cases with newly diagnosed breast diseases or normal tissue). Neither total PCB serum concentrations (nine congeners) nor groups of congeners were associated with breast cancer risk. More specifically, the total concentrations of "potentially anti-estrogenic and dioxin-like" congeners (PCB 74, PCB 118, PCB 138, PCB 156, PCB 170) were not associated with breast cancer risk. Using a comparable grouping scheme (congeners 118, 138, 156, 170), we found no association in our data set either (OR = 1.31, 95 percent CI: 0.72, 2.34; fourth vs. first quartile). Zheng et al. (14) did not find any association in a second study involving breast adipose tissue instead of serum for PCB analysis. However, the authors reanalyzed their data using logistic ridge regression analysis and demonstrated a protective effect on breast cancer risk for PCB 156, while PCB 180 and PCB 183 were associated with an increased risk (16).

In contrast, Aronson et al. (17) reported an association between the concentration of either PCB 105 (OR = 3.17, 95 percent CI: 1.51, 6.68; fourth vs. first quartile) or PCB 118 (OR = 2.31, 95 percent CI: 1.11, 4.78; fourth vs. first quartile) measured in breast adipose tissue and breast cancer risk, in a case-control study involving 217 cases and 213 controls with benign breast disease. However, no association between PCB 118 in breast adipose tissue and breast cancer

risk was observed in a study from Long Island, New York, involving 232 cases and 323 hospital controls admitted to surgery for benign breast disease or other diseases (18). In a Norwegian study with 150 cases and 150 controls, Ward et al. (19) also did not note an association between breast cancer risk and the concentration of PCB 118 measured in serum samples that were collected 2 years or more prior to diagnosis.

Smaller studies also provided some evidence of a link between dioxin-like congeners and breast cancer risk. Liljegren et al. (8) reported an increased risk of breast cancer among women with the highest breast adipose tissue levels of non-*ortho* coplanar congeners PCB 77 (OR = 2.9, 95 percent CI: 0.5, 15) and PCB 169 (OR = 3.4, 95 percent CI: 0.5, 18). Güttes et al. (9) reported significantly higher concentrations of PCB 118 in breast adipose tissue of cases than in that of controls. Finally, concentrations of PCB 28 and PCB 52 in breast fat were associated with malignant lesions in a study involving 69 women with breast cancer and 65 women with benign breast disease (20).

Our study is therefore the second large case-control study to note a positive association between mono-*ortho* PCBs and breast cancer risk. It is worthwhile mentioning that the same laboratory conducted PCB analyses in our study and those of Aronson et al. (17). This laboratory has a large amount of experience in conducting congener-specific PCB analyses and has repeatedly obtained excellent results in interlaboratory quality assurance and control programs. Furthermore, this laboratory reaches detection limits of 0.02 μg/liter in plasma for most PCB congeners, including mono-*ortho* PCBs, whereas higher detection limits are often reported by other laboratories conducting these analyses (5, 10, 13). Hence, we might speculate that the random error associated with the determination of mono-*ortho* congeners may be lower for this laboratory compared with others involved in similar studies, which had allowed us and Aronson's group to observe these associations.

Our results may indicate a relation between dioxin-like compounds and breast cancer risk. Although only three dioxin-like compounds (mono-*ortho*-substituted PCBs) were analyzed in this study, we previously showed that PCB 105, PCB 118, and PCB 156 represent a major fraction of the total TEQ concentration in milk samples from the southern Quebec population (49). Furthermore, the total dioxin-like compound concentrations (including 2,3,7,8-polychlorodibenzo-*p*-dioxins, 2,3,7,8-polychlorodibenzofurans, and non- and mono-*ortho* PCB congeners, expressed in TEQ) were highly correlated to the total concentrations of the three mono-*ortho* congeners also expressed in TEQ (Spearman's $r = 0.91$, $p < 0.0001$) in 25 breast milk samples from southern Quebec (É. Dewailly, unpublished data). Hence, mono-*ortho* PCBs constitute a good indicator of all dioxin-like compounds in our population, and the latter may constitute a risk factor for breast cancer.

One mechanism by which dioxin-like compounds might increase breast cancer risk is through the induction of biotransformation enzymes that may in turn affect estradiol metabolism (39). For example, non-*ortho* congener PCB 169 was shown to induce CYP1A1 and CYP1B1 but not estradiol metabolism when tested in MCF-7 or HepG2 cells, whereas non-*ortho* congener PCB 126 induced both enzymes and estradiol metabolism (42). Other studies showed that CYP1A, CYP3A, and CYP1B1 enzyme induction increases the formation of 4-hydroxy-estradiol, a catechol estrogen that produces DNA damage through the formation of reactive free radicals (43).

Alternatively, plasma lipid levels of mono-*ortho* PCB congeners may not be causally related to the disease but may be an indicator of women metabolically predisposed to breast cancer. In contrast to PCB 153 that is highly refractory to metabolism (50), plasma lipid concentrations of more easily metabolized congeners such as PCB 105 or PCB 118 reflect in part the activities of

enzymes involved in their biotransformation (24). The higher the activities of biotransformation enzymes in a person (due to genetic polymorphisms or dietary/lifestyle habits), the lower are the concentrations of these congeners. Further supporting this statement, we previously reported in a group of fish eaters environmentally exposed to PCBs that plasma lipid concentrations of mono-*ortho* congeners PCB 105 and PCB 118 were inversely correlated to liver CYP1A2 activity, which was itself induced by smoking (51). In this study, the mean plasma concentration of PCB 118 was 40 percent lower in heavy smokers compared with that in nonsmokers (13.1 vs. 21.5 μg/kg of lipids; $p < 0.05$). Perhaps plasma lipid concentrations of PCB 105 and PCB 118 indicate a particular profile of biotransformation enzyme, mainly defined by elevated CYP1A/1B1 activities, which could affect circulating levels of estrogens, a known risk factor for breast cancer (52). Further studies are needed to identify which cytochrome P450 enzymes are involved in mono-*ortho* PCB metabolism and how these enzymes may modulate circulating levels of estrogens and their metabolites in women.

In conclusion, our results and those obtained in a previous Canadian study suggest a relation between plasma concentrations of mono-*ortho* PCB congeners and breast cancer risk. Although levels of these dioxin-like compounds may represent a risk factor for the disease, additional studies are needed before concluding that these compounds are causally involved in the etiology of breast cancer.

ACKNOWLEDGMENTS

This work was supported by grant 4811-82 from the National Cancer Institute of Canada.

The authors are indebted to the nurses who participated in this study, to Andrée Christen who supervised the data collection, and to Dr. Jean-Philippe Weber, Dr. Liliane A. Ferron, and Évelyne Pelletier for organochlorine analyses.

REFERENCES

1. Falck F Jr, Ricci A, Wolff MS, et al. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. Arch Environ Health 1992;47:143–6. Bibliographic Links Library Holdings [Context Link]

2. Wolff MS, Toniolo PG, Lee EW, et al. Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 1993;85:648–53. [Context Link]

3. Krieger N, Wolff MS, Hiatt RA, et al. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. J Natl Cancer Inst 1994;86:589–99. [Context Link]

4. Hunter DJ, Hankinson SE, Laden F, et al. Plasma organochlorine levels and the risk of breast cancer. N Engl J Med 1997;337:1253–8. [Context Link]

5. Høyer AP, Grandjean P, Jørgensen T, et al. Organochlorine exposure and risk of breast cancer. Lancet 1998;352:1816–20. Bibliographic Links Library Holdings [Context Link]

6 Millikan R, DeVoto E, Duell EJ, et al. Dichlorodiphenyl-dichloroethene, polychlorinated biphenyls, and breast cancer among African-American and white women in North Carolina. Cancer Epidemiol Biomarkers Prev 2000;9:1233–40. [Context Link]

7. Laden F, Collman G, Iwamoto K, et al. 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)ethylene and polychlorinated biphenyls and breast cancer: combined analysis of five U.S. studies. J Natl Cancer Inst 2001;93:768–76. Bibliographic Links Library Holdings [Context Link]

8. Liljegren G, Hardell L, Lindstrom G, et al. Case-control study on breast cancer and adipose tissue concentrations of congener specific polychlorinated biphenyls, DDE and hexachlorobenzene. Eur J Cancer Prev 1998;7:135–40. [Context Link]

9. Güttes S, Failing K, Neumann K, et al. Chlororganic pesticides and polychlorinated biphenyls in breast tissue of women with benign and malignant breast disease. Arch Environ Contam Toxicol 1998;35:140–7. **Bibliographic Links Library Holdings** [Context Link]

10. Moysich KB, Ambrosone CB, Vena JE, et al. Environmental organochlorine exposure and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 1998;7:181–8. **Bibliographic Links Library Holdings** [Context Link]

11. Dorgan JF, Brock JW, Rothman N, et al. Serum organochlorine pesticides and PCBs and breast cancer risk: results from a prospective analysis (USA). Cancer Causes Control 1999;10:1–11. **Bibliographic Links Library Holdings** [Context Link]

12. Helzlsouer KJ, Alberg AJ, Huang HY, et al. Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. Cancer Epidemiol Biomarkers Prev 1999;8:525–32. [Context Link]

13. Zheng T, Holford TR, Mayne ST, et al. Risk of female breast cancer associated with serum polychlorinated biphenyls and 1,1-dichloro-2,2'-bis(*p*-chlorophenyl)ethylene. Cancer Epidemiol Biomarkers Prev 2000;9:167–74. [Context Link]

14. Zheng T, Holford TR, Tessari J, et al. Breast cancer risk associated with congeners of polychlorinated biphenyls. Am J Epidemiol 2000;152:50–8 [Context Link]

15. Wolff MS, Zeleniuch-Jacquotte A, Dubin N, et al. Risk of breast cancer and organochlorine exposure. Cancer Epidemiol Biomarkers Prev 2000;9:271–7. [Context Link]

16. Holford TR, Zheng T, Mayne ST, et al. Joint effects of nine polychlorinated biphenyl (PCB) congeners on breast cancer risk. Int J Epidemiol 2000;29:975–82. [Context Link]

17. Aronson KJ, Miller AB, Woolcott CG, et al. Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2000;9:55–63. **Bibliographic Links Library Holdings** [Context Link]

18. Stellman SD, Djordjevic MV, Britton JA, et al. Breast cancer risk in relation to adipose concentrations of organochlorine pesticides and polychlorinated biphenyls in Long Island, New York. Cancer Epidemiol Biomarkers Prev 2000;9:1241–9. [Context Link]

19. Ward EM, Schulte P, Grajewski B, et al. Serum organochlorine levels and breast cancer. a nested case-control study of Norwegian women. Cancer Epidemiol Biomarkers Prev 2000;9:1357–67. **Bibliographic Links Library Holdings** [Context Link]

20. Lucena RA, Allam MF, Costabeber IH, et al. Breast cancer risk factors: PCB congeners. Eur J Cancer Prev 2001;10:117–19. **Ovid Full Text Bibliographic Links Library Holdings** [Context Link]

21. Brinkman UAT, De Kok A. Production, properties and usage. In: Kimbrough RD, ed. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam, NY: Elsevier/North-Holland Biochemical Press, 1980:1–40. [Context Link]

22. Schulz DE, Patrick G, Dulnker JC. Complete characterization of polychlorinated biphenyl congeners in commercial Aroclor and Clophen mixtures by multidimensional gas chromatography-electron capture detection. Environ Sci Technol 1989;29:852 -9. **Bibliographic Links Library Holdings** [Context Link]

23. Newsome WH, Davies DJ, Sun WF. Residues of polychlorinated biphenyls (PCB) in fatty foods of Canadian diet. Food Addit Contam 1998;15:19–29. **Bibliographic Links Library Holdings** [Context Link]

24. Brown JF Jr, Lawton RW, Ross MR, et al. Persistence of PCB congeners in capacitor workers and Yusho patients. Chemosphere 1989;19:829–34. **Bibliographic Links Library Holdings** [Context Link]

25. Lordo RA, Dinh KT, Schwemberger JG. Semivolatile organic compounds in adipose tissue: estimated averages for the US population and selected subpopulations. Am J Public Health 1996;86.1253–9. Ovid Full Text Bibliographic Links Library Holdings [Context Link]

26. Lebel G, Dodin S, Ayotte P, et al. Organochlorine exposure and the risk of endometriosis. Fertil Steril 1998;69·221–8. Bibliographic Links Library Holdings [Context Link]

27. Dewailly É, Ayotte P, Lalıberté C, et al. Polychlorinated biphenyl (PCB) and dichlorodiphenyl (DDE) concentrations in the breast milk of women in Quebec. Am J Public Health 1996;86:1241–6. [Context Link]

28. Ecobichon DJ, MacKenzie DO. The uterotropic activity of commercial and isomerically-pure chlorobiphenyls in the rat. Res Commun Chem Pathol Pharmacol 1974;9:85–95. Bibliographic Links Library Holdings [Context Link]

29. Gellert RJ. Uterotrophic activity of polychlorinated biphenyls (PCB) and induction of precocious reproductive aging in neonatally treated female rats. Environ Res 1978;16:123–30. Bibliographic Links Library Holdings [Context Link]

30. Nesaretnam K, Corcoran D, Dils RR, et al. 3,4,3',4'-Tetrachlorobiphenyl acts as an estrogen in vitro and in vivo. Mol Endocrinol 1996;10:923–36. Bibliographic Links Library Holdings [Context Link]

31. Bandiera S, Safe S, Okey AB. Binding of polychlorinated biphenyls classified as either phenobarbitone-, 3-methylcholanthrene- or mixed-type inducers to cytosolic Ah receptor. Chem Biol Interact 1982;39:259–77. Bibliographic Links Library Holdings [Context Link]

32. Safe S, Astroff B, Harris M, et al. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds as antioestrogens: characterization and mechanism of action. Pharmacol Toxicol 1991;69:400–9. Bibliographic Links Library Holdings [Context Link]

33. Zacharewski T, Harris M, Safe S. Evidence for the mechanism of action of the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-mediated decrease of nuclear estrogen receptor levels in wild-type and mutant mouse Hepa 1c1c7 cells. Biochem Pharmacol 1991;41:1931–9. Bibliographic Links Library Holdings [Context Link]

34. Chaloupka K, Krishnan V, Safe S. Polynuclear aromatic hydrocarbon carcinogens as antiestrogens in MCF-7 human breast cancer cells: role of the Ah receptor. Carcinogenesis 1992;13:2233–9. Bibliographic Links Library Holdings [Context Link]

35. Harris M, Zacharewski T, Safe S. Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and related compounds on the occupied nuclear estrogen receptor in MCF-7 human breast cancer cells. Cancer Res 1990;50:3579–84. Bibliographic Links Library Holdings [Context Link]

36. Krishnan V, Safe S. Polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins (PCDDs), and dibenzofurans (PCDFs) as antiestrogens in MCF-7 human breast cancer cells: quantitative structure-activity relationships. Toxicol Appl Pharmacol 1993;120.55–61. Bibliographic Links Library Holdings [Context Link]

37. Safe SH. Polychlorinated biphenyls (PCBs): environment impact, biochemical and toxic responses, and implications for risk assessment Crit Rev Toxicol 1994;24:87–149. Bibliographic Links Library Holdings [Context Link]

38. Spink DC, Eugster HP, Lincoln DW 2nd, et al. 17-Beta-estradiol hydroxylation catalyzed by human cytochrome P450 1A1: a comparison of the activities induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in MCF-7 cells with those from heterologous expression of the cDNA. Arch Biochem Biophys 1992;293.342–8. Bibliographic Links Library Holdings [Context Link]

39 Martucci CP, Fishman J. P450 enzymes of estrogen metabolism. Pharmacol Ther 1993;57:237–57. Bibliographic Links Library Holdings [Context Link]

40. Hayes CL, Spink DC, Spink BC, et al. 17-Beta-estradiol hydroxylation catalyzed by human cytochrome P450 1B1. Proc Natl Acad Sci U S A 1996;93:9776–81. Bibliographic Links Library Holdings [Context Link]

41 van der Burght ASA, Cluysters PJ, Horbach GJ, et al. Structure-dependent induction of CYP1A by polychlorinated biphenyls in hepatocytes of Cynomolgus monkeys (*Macaca fascicularis*). Toxicol Appl Pharmacol 1999;155·13–23.

Bibliographic Links Library Holdings [Context Link]

42. Pang SK, Cao JQ, Katz BH, et al. Inductive and inhibitory effects of non-*ortho*-substituted polychlorinated biphenyls on estrogen metabolism and human cytochromes P450 1A1 and 1B1. Biochem Pharmacol 1999;58:29–38. **Bibliographic Links Library Holdings** [Context Link]

43. Liehr JG. Is estradiol a genetic mutagenic carcinogen? Endocr Rev 2000;21:40–54. **Ovid Full Text Bibliographic Links Library Holdings** [Context Link]

44. Connor K, Safe S, Jefcoate CR, et al. Structure-dependent induction of CYP2B by polychlorinated biphenyl congeners in female Sprague-Dawley rats. Biochem Pharmacol 1995;50:1913–20. **Bibliographic Links Library Holdings** [Context Link]

45. Denison MS, Whitlock JP Jr. Xenobiotic-inducible transcription of cytochrome P450 genes. J Biol Chem 1995;270:18175–8. **Bibliographic Links Library Holdings** [Context Link]

46. Huang Z, Guengerich FP, Kaminsky LS. 16-Alpha-hydroxylation of estrone by human cytochrome P4503A4/5. Carcino-genesis 1998;19:867–72. [Context Link]

47. Demers A, Ayotte P, Brisson J, et al. Risk and aggressiveness of breast cancer in relation to plasma organochlorine concentrations. Cancer Epidemiol Biomarkers Prev 2000;9:161–6. [Context Link]

48. Van den Berg M, Birnbaum L, Bosveld ATC, et al. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ Health Perspect 1998;106:775–92. **Bibliographic Links Library Holdings** [Context Link]

49. Dewailly É, Weber JP, Gingras S, et al. Coplanar PCBs in human milk in the province of Québec, Canada: are they more toxic than dioxin for breast fed infants? Bull Environ Contam Toxicol 1991;47:491–8. **Bibliographic Links Library Holdings** [Context Link]

50. Muhlebach S, Wyss PA, Bickel MH. The use of 2,4,5,2',4',5'-hexachlorobiphenyl (6-CB) as an unmetabolizable lipophilic model compound. Pharmacol Toxicol 1991;69:410–15. **Bibliographic Links Library Holdings** [Context Link]

51. Ayotte P, Dewailly É, Lambert GH, et al. Liver P4501A2 activity in individuals from fishing communities along the Gulf of St. Lawrence (Québec, Canada). In: Fiedler H, Frank H, Hutzinger O, et al, eds Dioxin '93, 13th International Symposium on Chlorinated Dioxins and Related Compounds. Vienna, Austria: Federal Environmental Agency, Austria, 1993:47–50. [Context Link]

52. Hankinson SE, Willett WC, Manson JE, et al. Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. J Natl Cancer Inst 1998;90:1292–9. [Context Link]

breast neoplasms; case-control studies; estrogens; polychlorinated biphenyls

Accession Number: 00000429-200204010-00007